ORIGINAL ARTICLES

GASTRO-INTESTINAL DISEASES: THE NEWER THERAPY*

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THE great problem in summarizing the so-called "modern advances" in a selected field of medicine is to determine what is new and what is old! When we stop and analyze an accomplishment in the solution of the nature of a disease or the method of a revolutionary therapeutic procedure, we find that it did not spring into being, but grew slowly from many small beginnings. Before a practicable and utilizable understanding was reached, there were many isolated and contributing experiments, with various additions and data from many sources.

And so, in mentioning what we may choose to call the examples of our newer knowledge and therapy in gastro-enterology, it can readily be seen that each, in various parts and forms, has been talked and written about for several previous years. There is usually quite a literature on the subject before general acceptance has occurred. This has been particularly true in the development of the use of vitamin K in the bleeding of jaundice; of the therapy of peptic hemorrhage; and recognition of the importance of gastroscopy. There is nothing new under the sun!

Some of the most interesting advances, both clinical and in the field of research, concern the causes and treatment of peptic ulcer. It is true that the etiologic nature of this chronic disease is still undetermined; but modern knowledge has shown that we cannot view this affection simply as a local disease limited to the stomach and duodenum alone, but as an inherent tendency in the constitutional make-up of the particular individual. Though the fundamental cause may not be known, we now recognize three primary etiologic factors:

1. Local tissue injury of the stomach or duodenum.
2. The eroding action of acid-pepsin chyme.
3. The neurogenic background (both psychic and autonomic).

In treating peptic ulcer, a therapeutic régime directed toward the control of these three factors is essential. Tissue injury is prevented by eliminating focal infections about the head, in the gallbladder, genito-urinary tract, and by protection from seasonal respiratory infections. Nutritional tissue injury such as may result from a deficiency in vitamins C and B, particularly when on limited diets, or the actual trauma produced by ingested liquids, drugs, or coarse foods, must be rectified. Allergic tissue injury producing ulcer has never been proved. Justification for treatment with the more or less popular parenteral injections has depended somewhat upon the allergic theory as a causative factor in peptic ulcer. Now, modern research has shown that the temporary benefit of such procedures is probably psychologic, and can be paralleled by a change of environment. Almost any striking method for the treatment of peptic ulcer has been of transient benefit, but the consensus of opinion of reliable investigators has been that the parenteral method is not indicated in the routine treatment of peptic ulcer.

The effect of certain hormones in protecting the local tissues of the stomach and duodenum, either directly or trophically, has been the subject of considerable research. An assumption that pituitary deficiency exists has led to a method of treatment with a fresh pituitary preparation of the posterior lobe, given hypodermically, orally, or intranasally. However, from the reports it is obvious that this method has produced only a temporary healing effect on the ulcer, and we must await further proof that such therapy is of any real value. A much more convincing study on the relation of gonadotropic hormones to peptic ulcer has been reported by Sandweiss and his collaborators. It is known that pregnancy has a beneficial effect on the symptoms of peptic ulcer and that aggravation frequently occurs in the menopause. Daily injections of antuitrin S have protected Mann-Williamson dogs from developing peptic ulcer, while theelin had no effect. In treating humans the results were less favorable, but of course the amounts given in daily injections do not approximate the large amounts secreted in pregnancy. There can be no question but that gonadotropic hormone has some beneficial or soothing effect on the gastro-intestinal tract, and that includes the colon.

Further evidence that discrete intracranial lesions may be the cause of ulceration of the upper part of the digestive tract is found in observations made by Opper and Zimmerman, probably stimulated by the previous studies of Cushing. They feel that gastro-intestinal lesions in cases of cortical and mesencephalic involvement are most probably mediated through the hypothalmic nuclei. Lesions of the brain and alterations in hormonal activity in their effect on the autonomic nervous system and the gastro-intestinal tract will undoubtedly further intrigue investigators.

Controversial as all of the above-mentioned data may be, modern investigation has served only to make more certain that the second etiologic factor—the acid-pepsin chyme element as an eroding agent preventing the healing of peptic ulcer—stands unchallenged. By whatever method, it has been conclusively proved that the ulcerated tissue must be protected from this erosion. This can be done only partially by food and frequent feedings. However, it has become recognized that the acid element is chiefly important as the activator of the pepsin element, and that complete alkalinization is unnecessary to destroy the acid-pepsin combination. Palmer has shown that merely a control of the hydrogen ion of the stomach contents at a p^H of about 4, or even less, is an optimum level sufficient to secure clinical relief and produce healing; whereas, for the elimination of total acidity the p^H must be elevated to 7.

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The old Sippy method of alkalinization by the use of soluble alkalis did the latter, often producing alkalosis. Today we only attempt neutralization, reduction of the stomach p^H, by the use of non-soluble alkalis which do not disturb the acid base of the blood. The chief of these agents in the order of their neutralizing capacity are calcium carbonate, tricalsate, tribasic calcium, or magnesium phosphate and aluminum hydroxid.

Palmer has summarized the effect of these antacids in an interesting manner:

ANTACIDS

Listed in decreasing order of neutralizing capacity:

1. Calcium carbonate ..... 4 gms.
2. Calcium carbonate ..... 2 gms.
3. Sodium bicarbonate plus calcium carbonate aa ..... 2 gms.
4. Aluminum hydroxid ..... 30 c. c.
5. Tricalsate ..... 4 gms.
6. Tribasic calcium phosphate ..... 4 gms.
7. Aluminum hydroxid ..... 16 c. c.
8. Sodium bicarbonate ..... 4 gms.
9. Aluminum hydroxid ..... 4 c. c.
10. Magnesium trisilicate ..... 1 gm.

Atropin increases the neutralizing capacity of antacids. Furthermore, we have come to recognize that the peptic ulcer difficult to control is practically always associated with the phenomenon of hypersecretion, and that by combining sufficient amounts of atropin with our neutralizing powders this condition may be better controlled.

Finally, modern thought defines the limits that any of the above methods may have in bringing about a complete cure, and emphasizes the primary importance in considering the general systemic or nervous disturbances of the individual with ulcer. The mental and emotional makeup, the environment, social status, personal habits of life, psychic states, and autonomic tension must be corrected and relieved.

Of the complications of peptic ulcer, the optimum treatment of hemorrhage has created a wide divergence of opinion as to the details of therapeutic measures. Modern therapy has established, however, some fundamental principles which are now quite generally accepted, and which signalize real progress. Leading experience favors treatment of peptic hemorrhage by medical measures with few exceptions, and these are rare. It is conceded that massive hemorrhage, in persons under the age of forty-five years, involves relatively slight risk.

The policy of prolonged initial starvation is now considered definitely unwise. Since the reports of Professor E. Meulengracht before the Scandinavian Congress of Internal Medicine in 1933, citing only a one per cent mortality from peptic hemorrhage by a method of liberal feeding, there has gradually been an almost universal swing to early or immediate feeding after the hemorrhage. Research studies have shown that after massive hemorrhage there is an enormous toxic destruction of protein, with an elevation of the nonprotein nitrogen and urea, a tendency to uremia and tissue exhaustion, and great dehydration. Food, fluid, and blood are needed.

Meulengracht's purée diet allows three hourly feedings and includes cereals, bread, butter, tea, sliced meats, omelettes, fish, cheese, potatoes, puréed vegetables, vegetable soups, stewed fruits, and puddings, with very little restriction as to quantity. Here in America, as a rule, we have not been bold enough to follow the plan completely. Various modifications of this liberal dietary régime are used, but the fundamental principle of small frequent feedings of simple food, instituted without delay after the hemorrhage, seems to be agreed upon with few exceptions. It is probable that the details of the diet selections in such an emergency are of relatively minor importance. Morphin, bed rest, and quiet are of importance. Most hemorrhages stop abruptly. Extreme measures are unwise. Dehydration must be overcome by parenteral fluids. Transfusion is indicated for those in shock with hemoglobins of 50 per cent or less, or when bleeding continues. Liver extract injections, vitamins B and C parenterally, and glucose, given cautiously are helpful. When surgical measures are indicated, they usually should not be delayed beyond forty-eight hours after the start of the hemorrhage.

The subject of peptic irritation should not be dismissed without commenting upon some phases of hiatus hernia of the stomach through the diaphragm. This lesion is now being recognized with increasing frequency, and is commonly found with a short esophagus. Profuse and persistent hemorrhage, associated with peptic ulcer of the esophagus, are not unusual complications and need to be treated by a modified ulcer régime. I have frequently traced severe, unexplained anemias to this source.

The use of the flexible gastroscope, and the observations of Schindler and his pupils by this means, have certainly been one of the outstanding accomplishments in the field of gastro-enterology in recent years. The gastroscope in skillful hands not only has determined the nature of doubtful lesions in the stomach, but much more important, in my opinion, has made possible actual diagnosis of diffuse organic disease of the mucosa and wall of the stomach, which heretofore has been largely presumptive. This knowledge is narrowing our diagnoses of gastric neuroses. Atrophic, inflammatory, and degenerative changes are now proved. Gastritis as a cause of many of the dyspepsias is now becoming popular again, after having been banished in favor of functional disturbances. Atrophic and hypertrophic gastritis are found to exist as clinical entities.

Furthermore, there has been a tremendous impetus given to the treatment of diffuse disease of the stomach wall under the direct control of gastroscopic visualization. The effect of diet, of lavages with various agents such as hydrogen peroxid, reactions to colloidal kaolin in alumina gel or alumina gel alone, of vitamin B_1 and B_2, and vitamin C; and in the atrophic forms with or without anemia, the effect of liver therapy can be studied graphi-

cally. The peptic ulcer of hypertrophic gastritis can be seen and treated. Gastric distress following surgery of the stomach is commonly an unsolved problem. Now, by visualization, we have revealed a true postoperative gastritis, among other complications and lesions, which can be treated more intelligently. We are rapidly accumulating a wider knowledge in this field of medicine.

THE LIVER AND BILIARY SYSTEM

In the last several years we have added greatly to our knowledge in the differentiation of disorders of the liver and biliary system, especially in the understanding of hepatic physiology and in establishing fundamental principles of therapy. This is particularly true in the treatment of jaundice and cirrhosis of the liver.

The liver is a storehouse for glycogen. This glycogen store is depleted in jaundice and cirrhosis, so that the feeding of sugars and other carbohydrates, and, when needed, the intravenous administration of glucose has become a recognized treatment for hepatic disease and as a preliminary to all biliary tract surgery. Certainly, our chief therapeutic aid in the treatment of the cirrhoses and degenerative changes in the hepatic parenchyma is the high carbohydrate diet. However, it is becoming even more obvious that the success or failure of treatment of a patient who has a severely damaged liver depends to a large extent on the patient's ability to take a well-balanced and ample diet over a long period.

We have also learned that injurious fat accumulations develop as the glycogen content of the liver lessens. The relationship of the sugar and fat metabolism of the liver, and the appreciation of a reciprocal activity, the fat-glycogen antagonism, is evidently of the utmost importance for practical therapeutic purposes, not only in diabetes and acute diarrheic and depleting gastro-intestinal upsets, but also in the essential liver disorders mentioned above. Livers with low glycogen content have an increased susceptibility to injury and they also accumulate fat. It would appear, therefore, that the amount of fat ingestion by the alimentary canal, if it can be adequately handled by the gastro-intestinal tract, is not of such primary importance in the effect on the liver if there is an adequate carbohydrate intake which insures repletion of the liver glycogen.

The protein metabolism of the liver is exceedingly important, and the therapeutic use of proteins in the diet in liver disorders has aroused keen interest. For practical clinical purposes, the experimental reports in the literature present some conflicting conclusions. Dogs with jaundice, produced by tying off the common bile duct, develop ascites and edema when fed meat. This condition can be cured by stopping meat. On the other hand, patients with portal cirrhosis and ascites improve on high protein-carbohydrate diets. It has been rather generally assumed that in obstructive jaundice especially, and presumably in the more diffuse changes of toxic and degenerative hepatitis, the protein metabolism of the liver has become deficient, so that a low protein intake has been recommended. In jaundice, then, many recommend the elimination of meat protein and the use of dairy proteins (milk, cheese, egg white) and gelatines. In cirrhosis of the liver, especially with ascites, a quite high protein diet is advised to make up the loss of serum protein in the abdominal fluid, again with gelatin supplements, but with the question of the use of meat somewhat uncertain.

The liver is instrumental in the formation or storage of vitamins A, B_1 B_2 complex, C and D. These functions are disturbed considerably by injury to its parenchyma and the consequent reduction of bile acids in the intestine. Recently, Rich and Hamilton (Johns Hopkins Medical Bulletin) have reported the production of cirrhosis of the liver, of a type resembling Laennec's or portal cirrhosis in man, which occurred in rabbits on diets supplemented by various vitamins, but lacking yeast. Evidence indicated that the cirrhosis was due to the lack of some factor contained in yeast, but different from vitamins B_1, B_2, B_6 and nicotinic acid. Ascites occurred in half of the animals. The diet of the animals that developed cirrhosis was deficient in choline, whereas the animals that did not develop cirrhosis were obtaining choline from yeast. Fat accumulates in the livers of animals lacking choline in the diet. The experiments are interesting in view of the frequency of cirrhosis in chronic alcoholics, many of whom, as is well known, restrict their diet and develop symptoms due to vitamin deficiencies, notably pertaining to vitamins contained in yeast.

In portal cirrhosis then (and this means most of the clinical cases we treat), the feeding of vitamin concentrates with large amounts of whole vitamin B, especially all the elements contained in yeast, together with a high carbohydrate diet and at least 100 to 125 grams of protein in an attempt to elevate the plasma protein, has been surprisingly helpful in many cases. Intramuscular injections of liver extract appear also to have some direct effect on nitrogen balance and the retention of protein, as well as in combating the macrocytic anemia of liver disease so resistant to treatment. The administration of iron and repeated transfusions in the seriously ill patients are necessary adjuncts to treatment. These methods—and, if necessary, abdominal tapping as required for comfort—are, in my opinion, much more effective than omentopexy or the time-honored use of diuretics, such as acid-producing salts and mercurials. Needless to say, the first step, and the most important in treating the liver, is to stop the intake of liver toxins, be they alcohol, arsenic, or what not.

In my opinion, the most spectacular advance of the past year has been the use of vitamin K in the hemorrhage of jaundice. So-called "cholemic bleeding" has been an unsolved problem for years. It has been apparent that this complication was dependent on some intrinsic change in the coagulating properties of the blood. Recent evidence indicates that deficiency of the prothrombin of the blood is probably the essential feature. A series of brilliant investigations have shown that there are

two factors which maintain a normal prothrombin level in the blood, namely, the presence of a certain bile acid, deoxycholic acid, and a fat-soluble vitamin known as vitamin K (plentiful in the food we feed our cattle, such as alfalfa and other grasses). By bringing these two together in the intestinal tract of the jaundiced patient, an elevated prothrombin time is speedily reduced to normal limits, with a striking inhibitory effect on actual bleeding. Errors have been made in feeding the proper bile constituent, which is deoxycholic acid. Discomfort in seriously ill patients in feeding the Klotogen or vitamin K tablets and the numerous bile pills has been a handicap, but now we have vitamin K ready for intravenous use and the bile acid need not be given, truly a boon of the highest order for the harassed surgeon in these difficult cases.

THE SMALL INTESTINE

Diseases of the small bowel in the past have quite uniformly gone unrecognized unless obstruction developed. All too frequently our first intimation of pathology in this region comes with the onset of one of the most dramatic crises in abdominal emergencies. In recent years there has been increased interest in the small intestine because of the development of a better clinical approach in diagnosis, and of a better understanding of the physiology of this portion of the intestine. While localizing symptoms are meager at first, we have learned the importance in this respect of a complaint of persistent umbilical distress, irregular bouts of high distention, and the appearance of movable and changing distended loops and tumors. Improved methods of roentgenologic examination, afforded by plain films taken in various positions—prone, supine, and upright—disclosing collections of trapped gas and hairpin turns, and frequent fluoroscopic viewings of the progress of the barium meal, have been very enlightening. Use of the double tube, with intubation of the small intestine, is becoming a more common procedure. By all of these means more accurate diagnoses are now made than previously.

The problems of intestinal ileus, chronic stenosing inflammation, and absorptive functions in relation to carbohydrates, proteins, fats, and fluids, are arousing more interest than the detection of the various tumors of the small bowel. Modern therapy has emphasized the difference in the indications for treatment of mechanical ileus (obstruction) as opposed to paralytic ileus (adynamic). Although, on the one hand, there is an occlusion to be relieved, and, on the other, an atonic condition of the bowel muscle to overcome, both have the same features of distended gut, increased intraintestinal pressure, changes in blood chemistry, and toxemia. Both types of ileus may benefit from decompression of the distended bowel by means of a tube passed down through the mouth and stomach. An abdominal operation is useful only when there is a definite mechanical obstruction to be relieved, except as it may be required for an existing peritonitis. Yet, in practice, such operations are still being done in many places on paralytic ileus. An atonic intestine will not empty itself effectively until its peristaltic power is restored. Enterostomy in these cases is not approved. The use of pitressin, pituitrin, prostigmin, according to need, and if not contraindicated by peritonitis, of hypertonic saline by vein and rectum, and normal salt under the skin, are the primary aids in this endeavor and in the restoration of the water balance and normal blood chemistry. The proper use of the Miller-Abbott tube signalizes a great advance in the therapy of ileus. A summary of the advantages in its use is best expressed by quoting Abbott himself:

"The great contraindication to intubation is gangrene, and therefore success with the procedure demands excellent clinical judgment. On the other hand, a patient who has shown paralytic ileus from the start may undergo intubation successfully because, as the stomach, the duodenum, and the subsequent sections of small bowel are deflated, each in turn regains its peristaltic activity and forces the balloon onward. Striking relief of pain and shock follow, and normal motor function is restored. The advantages include emptying the intestine and restoring peristalsis, identification of the location and nature of the lesion with possibility of relief of obstruction, and the conversion of an emergency into an elective surgical procedure. Time is gained for further study and for insuring proper nourishment of the patient."

Ileitis or cicatrizing enteritis continues to be a diagnostic problem and a therapeutic nightmare. Although we are learning more of its clinical manifestations, we know nothing of its medical treatment. We all deplore the necessity of the radical resection of the diseased bowel, and several authors are now voicing more conservatism in favor of procedures which would usually be considered inadequate, such as appendectomy, enterostomy, or side tracking colostomy, with reports of delayed recurrences extending to five years. As a causative factor, the importance of resecting the mesenteric lymphatics is also being emphasized.

From the medical standpoint diffuse disturbances of the small intestine are manifested by abdominal discomfort, distention, and diarrhea—all of which are most difficult to relieve. Some suggestions as to therapeutic procedures have been gleaned by studying conditions which have arisen after bowel resection. In 1912, Joseph M. Flint (Professor of Surgery at Yale) reported in the Johns Hopkins Bulletin that about 50 per cent of the small intestine may be resected without much danger of serious consequences in the majority of cases. However, severe diarrhea, thirst, loss of weight, and loss of nitrogen and fat in the stools resulted, until secondary hypertrophy and hyperplasia of the remaining intestine took place. The carbohydrates were well absorbed. In the resections for ileitis, diarrhea becomes a troublesome complication.

Some light on the physiologic and nutritional disturbances resulting from loss of a large part of the small intestine has been supplied by the studies of West and coworkers on an individual, with three feet of small intestine remaining after

multiple resections for ileitis. Diarrhea, tetany, and abdominal distention were the clinical findings. Chemical studies showed that the blood calcium was very low, and that 45 per cent of the ingested fat was lost in the feces, a large proportion as free fatty acids, accounting for the large loss of calcium in the feces as calcium soaps. (It is to be remembered that calcium and phosphorous are absorbed in the small intestine.) Twenty-five per cent of the ingested protein was lost in the feces, but the assimilation of carbohydrate was found to be normal. One-fourth of the total caloric intake was lost in the stools. With only about one-sixth of his small bowel remaining (this being thickened and hypertrophied) this individual led a fairly satisfactory existence on a high carbohydrate, high protein diet, with extra calcium and viosterol feedings and low fat.

Studies and observations in sprue indicate that about the same type of disturbance takes place, and that defective absorption or utilization of essential food factors in the small bowel are evidently of major etiologic importance, as shown by the ineffectiveness of liver extract by mouth and the dramatic improvement when injected parenterally.

In sprue there is defective fat absorption, defective absorption, and a loss of calcium and poor utilization of vitamin D, as well as other essential food constituents.

Characteristic roentgenologic changes have been demonstrated in the small intestine in sprue, consisting of abnormal mucosal markings, increased segmentation, pocketing and stasis in isolated loops, as illustrated by the findings of Mackie, Miller, and Rhoads. These abnormalities may be seen to regress under specific therapy. In summary, apparently nature has provided the human with a safe excess of small intestine. Fat absorption would appear to be the chief limiting need for anything like the normal length of small gut. The maintenance of nutrition and control of diarrhea in any profound disturbance in the mechanism and physiology of this region apparently requires a high carbohydrate, high protein diet with very little fat; an intake of at least 10 to 12 grams of calcium; more and better utilization of vitamin D; and often injections of liver and possibly vitamin B. It is to be remembered, also, as shown by Althausen, that thyroid substance or thyroxin markedly increases the absorption of carbohydrates in the small intestine.

THE LARGE INTESTINE

Therapeutic advances in treating colon disease have been of chief interest in those disorders involving the large bowel as a whole. Surgeons have improved their technique and approach in handling circumscribed lesions, but completely satisfactory treatment of the diffuse disturbances has not been accomplished.

The tendency now, except in such diseases as the acute dysenteries, tuberculosis, amebiasis, and the rectal lesions of lymphogranuloma venereum, is to relegate infection to a secondary rôle, and elevate intrinsic abnormal activity in the bowel wall, in the musculature and autonomic nervous system, as causative factors. For instance, Lium discusses the possibility that ulcerative colitis may be conceived as a specific reaction to a number of influences which can initiate spasm of the colon musculature. Once the colon becomes spastic, it is an organ that can produce damage to its own surface. Spasm results in damage to the overlying epithelium with resultant hemorrhage and ulceration at times. Dysentery toxin produces ulceration through the injurious effects of smooth muscle spasm. Thus, hyperactivity of the parasympathetic nervous system, plus an insult such as bacillary dysentery, or one of our so-called "intestinal flus" and a final resultant vitamin deficiency, which occurs in all prolonged digestive disturbances, may explain the vagaries of ulcerative colitis. Exhaustion of the secretion of mucus, together with nutritional deficiency, may contribute to the prevention of healing. Vitamin B and liver extracts are not specifics for such disorders. Lerner and Rapaport have shown that avitaminosis A constitutes one of the complications found in this disease. Therefore, we must conclude that chronic ulcerative colitis appears to be the complex expression of the interaction of several different factors, as expressed by Mackie.

We have been flooded with drugs used to lessen the tone of the musculature of the bowel. Recent experiments have shown that atropin is just as effective an antispasmodic as syntropan, trasentin, and benzedrin sulfate, and probably better when given by mouth. Glyceryl trinitrate, amyl nitrite, pitocin and papaverin hydrochlorid are effective in relieving spasm, producing immobilization and putting the large intestine at rest.

On the other hand, increase in tone followed the use of morphin, physostigmin, acetylcholin and hypertonic salt solution. There is some question as to whether calcium salts do not increase rather than allay intestinal tone. Marked stimulation of colonic motility is produced by physostigmin and ephedrin together, and also by physostigmin and acetylcholin given simultaneously. Hypertonic solutions of glucose have no effect on colonic motility.

The favorable effect of gums and other hygroscopic substances, such as karaya gum, as nonirritating aids in overcoming spastic constipation, seems proved experimentally and practically. Pectin in its various forms, as apple or banana powder, etc., while helpful in some of the diarrheas, has not proved much more beneficial than any of our other less expensive substances. Recent work has shown the value of nickel pectinate, and indicates the possibility that some of the metal pectinates may be valuable therapeutic aids. Sulfanilamide in its various forms may be of help occasionally in intestinal infections if used judiciously for short periods; but it has not accomplished results such as it has in pneumonias or urinary infections.

Many authors have discussed in the past few years the functional or sociologic disorders of the colon, and point out that the vast majority of colon disturbances are undoubtedly functional and should be treated as such.

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